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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/535,268

03/21/2006

Keiji Kubo

08279.1210USWO

3871

52835

7590

11/12/2008

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EXAMINER

MCDOWELL, BRIAN E

ART UNIT

PAPER NUMBER

1624

MAIL DATE

DELIVERY MODE

11/12/2008

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/535,268	Applicant(s) KUBO ET AL.	
	Examiner BRIAN MCDOWELL	Art Unit 4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on 10/30/2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-29 and 33-37 is/are pending in the application.
- 4a) Of the above claim(s) 26-29 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-9, 11, 19, 21-25 and 33-37 is/are rejected.
- 7) ☒ Claim(s) 4, 10, 12-18, 20 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☒ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date <u>9/19/2006, 11/27/2006</u> . | 6) <input type="checkbox"/> Other: _____ |

BEM

DETAILED ACTION

Applicant's election with traverse of Group I (now drawn to claims 1-25 and 33-37) and election of specie (example 68) in the reply filed on 10/30/2008 is acknowledged. Claims 26-29 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Claims 27-29 are now part of Group VIII (along with the methods of making). The non-elected subject matter reserves the right to rejoinder if the compound claims are found allowable. Applicant timely **traversed** the restriction (election) requirement in the reply filed on 10/30/2008. The traversal is on the ground(s) that restriction within a single claim is improper. This is not found persuasive because the inventions did not have a single inventive concept as evidenced by the previous examiner. In addition, due to the complex variability of the genus structure shown in formula I, a search burden would exist if a restriction requirement was not implemented.

The requirement is still deemed proper and is therefore made FINAL.

This application contains claims drawn to an invention nonelected with traverse in the reply filed on 10/30/2008. A complete reply to this action must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's elected specie was found to be free of the prior art, thus the full scope of the claims will be examined.

An action on the merits of claims 1-25 and 33-37 is contained herein.

Priority

This application claims the priority date of 11/22/2002. However, a certified English version of the foreign priority document was not received.

Thus, the effective filing date of this application is 11/20/2003.

Abstract

The abstract of the disclosure is objected to because it is over the 150 word limit. Please limit the number of words and have the abstract represent the elected invention. Correction is required. See MPEP § 608.01(b).

Claim Objections

Claims 22-25 and 34-37 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. **The for use limitations are not considered and hold no patentable weight.**

Claim 20 is objected to because of the following informality: on page 8, line 5 at the far right, it says "6-choloro". The correct spelling should be "chloro". Please correct. Also, any compounds not embraced by the elected group should be removed.

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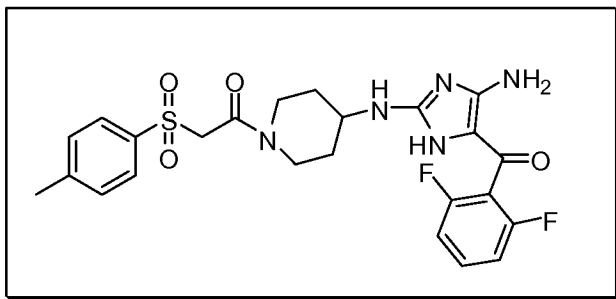
Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

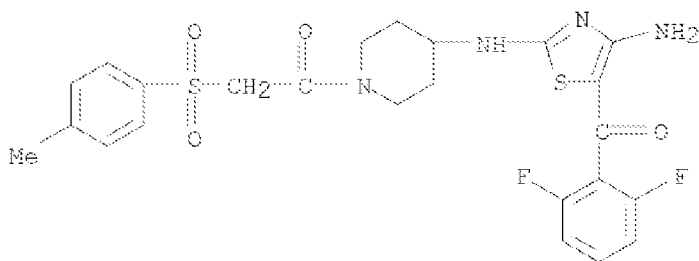
Claims 1-3,5-9,11,19,21-25, and 33-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chu *et al.* (WO 2005/0101595) in view of Patani *et al.* (Chem. Rev.).

The following compound may be drawn to the aforementioned claims:



wherein R¹ = H, B = substituted imidazole, W = a bond, and R = substituted aryl.

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Chu *et al.* teach the following compound:

wherein R¹ = H, B = substituted thiazole, W = a bond, and R = substituted aryl (see page 215, example R65).

The only difference between applicant's compound and the compound in the Chu document is the heterocycle B (specifically nitrogen being substituted for sulfur).

However, Patani teaches that in heterocyclic ring systems, -NH- is a common bioisotere for sulfur in medicinal chemistry (see page 3158, bottom of left column, Divalent Ring Equivalents section).

In summary, applicant is taking a known compound that is described in the literature and doing a simple modification to the molecule (-NH- for sulfur). One would have a reasonable expectation of success in obtaining a compound with biological activity upon this substitution. As mentioned before, the for use limitations in claims 22-25 and 34-37 hold no patentable weight. In addition, one of ordinary skill in the art would have been motivated to make a prodrug of this obvious compound (see enablement rejection below and references).

Therefore, applicant's compounds are obvious over the prior art and are rejected.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2 and 33-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts and prodrugs containing amide moieties of the claimed compounds, it does not reasonably provide enablement for making all prodrugs of the claimed compounds. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art of medicinal chemistry to use the invention. "The factors to be considered [in making an enablement rejection] have been summarized as :

- a) the quantity of experimentation necessary,
- b) the amount of direction or guidance presented,
- c) the presence or absence of working examples,
- d) the nature of the invention,
- e) the state of the prior art,
- f) the relative skill of those in that art,
- g) the predictability or unpredictability of the art,
- h) and the breadth of the claims",

In re Rainer, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

a) Finding a prodrug is an empirical exercise. Predicting if a certain ester of a claimed alcohol, for example, is in fact a prodrug, that produces the active compound metabolically, in man, at a therapeutic concentration and at a useful rate is filled with experimental uncertainty. Although attempts have been made to predict drug metabolism *de novo*, this is still an experimental science. For a compound to be a prodrug, it must meet three tests. It must itself be biologically inactive. It must be metabolized to a second substance in a human at a rate and to an extent to produce that second substance at a physiologically meaningful concentration. Thirdly, that second substance must be clinically effective. Determining whether a particular compound meets these three criteria in a clinical trial setting requires a large quantity of experimentation.

b) The direction concerning the prodrugs is not found in the specification.

c) There is no working example of a prodrug of a compound of the formula I other than those that contain amide moieties, particular carbamates. The disclosure does not provide guidance which would teach the skilled artisan in this field how to modify the core of the compound to obtain "prodrugs" which are other than amide containing prodrugs, particularly carbamates.

d) The nature of the invention are imidazoles. The modification of piperidine cores is not seen to be so routine and simple as to allow for the extrapolation of synthetic procedures which would attach amide moieties to the piperidine core to

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provide sufficient guidance to attach non-amide prodrug moieties to said piperidine cores.

e) Wolff (Medicinal Chemistry) summarizes the state of the prodrug art. Wolff, Manfred E. "Burger's Medicinal Chemistry, 5ed, Part I", John Wiley & Sons, 1995, pages 975-977. The table on the left side of page 976 outlines the research program to be undertaken to find a prodrug. The second paragraph in section 10 and the paragraph spanning pages 976-977 indicate the low expectation of success. In that paragraph the difficulties of extrapolating between species are further developed. Since, the prodrug concept is a pharmacokinetic issue, the lack of any standard pharmacokinetic protocol discussed in the last sentence of this paragraph is particularly relevant. Banker (Modern Pharmaceutics) Banker, G.S. et al, "Modern Pharmaceutics, 3ed.", Marcel Dekker, New York, 1996, pages 451 and 596. in the first sentence, third paragraph on page 596 states that "extensive development must be undertaken" to find a prodrug.

f) One would have a Ph. D. degree and several years of industrial experience.

g) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula I of claim 2 as well as the presently unknown list of potential prodrug derivatives embraced by the claims.

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MPEP 2164.01(a) states, "[a] conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to determine if any particular compound of unknown structure is, in fact, a prodrug.

Nowhere in the specification are directions given for preparing the "prodrugs" of the claimed compounds other than amide containing prodrugs. Since the structures of these "prodrugs" are uncertain, direction for their preparation must also be unclear. Directions to a team of synthetic pharmaceutical chemists and metabolism experts of how to search for a "prodrug" hardly constitute instructions to the BS process chemist of how to make such a compound.

Conclusion

No claims are allowed.

Claims 4,10, and 12-18 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Reasons for Allowance

Claim 4 is free of the prior art because the substituent R = naphthyl is a limitation that is not taught or fairly suggested by the closest prior art.

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Claims 10 and 12-18 are free of the prior art because the bicyclic system that is formed between the imidazole and NR¹ is a limitation that is not taught or fairly suggested by the closest prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRIAN MCDOWELL whose telephone number is (571)270-5755. The examiner can normally be reached on .

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BM

**/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624**